

General

Guideline Title

Evaluation of the adolescent or adult with some features of Marfan syndrome.

Bibliographic Source(s)

Pyeritz RE, American College of Medical Genetics and Genomics. Evaluation of the adolescent or adult with some features of Marfan syndrome. *Genet Med*. 2012 Jan;14(1):171-7. [23 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Evaluation for Marfan Syndrome (MFS)

MFS is characterized by autosomal dominant inheritance of features in the skeletal, ocular, cardiovascular, and pulmonary systems, along with muscular and adipose hypoplasia, dural ectasia, and hernias. As individuals with MFS live longer with aggressive and prophylactic management of their cardiovascular disease, additional features are emerging, such as renal and hepatic cysts. Because about one-third of patients have parents unaffected by MFS, more features are required in them to be certain of the diagnosis. Mutations in *FBNI*, the gene that encodes the large glycoprotein, fibrillin-1, cause MFS, but also cause many of the related conditions. Conversely, conditions that have been confused with MFS, such as congenital contractural arachnodactyly (CCA) and Loeys-Dietz syndrome (LDS), are due to mutations in genes that encode either related proteins (e.g., fibrillin-2) or proteins involved in pathogenesis of common features (e.g., TGF β receptors). There is no case of classic, bona fide MFS due to mutations in a gene other than *FBNI*. However, current clinical molecular testing of *FBNI* successfully detects mutations in such unequivocal patients in only about 90% to 95% of cases. For all of these reasons, searching for mutations in *FBNI* continues to have a circumscribed role in the diagnosis of equivocal cases. Said differently, MFS remains, by and large, a clinical diagnosis.

Diagnostic Criteria

If there is no family history of MFS, then the subject has the condition under any of the following four situations:

- A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area, i.e., a Z-score of $\geq +2$) and ectopia lentis
- A dilated aortic root and a mutation in *FBNI* that is clearly pathologic
- A dilated aortic root and multiple systemic features (see below) or
- Ectopia lentis and a mutation in *FBNI* that has previously been associated with aortic disease

If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:

- Ectopia lentis
- Multiple systemic features (see below) or
- A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

The scoring system for systemic features involves the following:

- Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hindfoot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced upper-to-lower segment ratio AND increased arm/height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (three of five including dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia) = 1
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1
- Maximum total: 20 points; score of 7 or more indicates systemic involvement

Diagnostic Evaluation

1. Physical exam
2. Family history
3. Echocardiogram
4. Dilated eye exam
5. Consider computed tomography (CT) or magnetic resonance imaging for evidence of lumbosacral dural ectasia and protrusion acetabula
6. Consider *FBN1* gene sequencing

Management

Cardiovascular: (recommend management by a skilled cardiologist)

A. *Aortic root dilation and/or diagnostic criteria met for MFS:*

- Annual echocardiogram for root diameter <4.5 cm in an adult and rate of increase <0.5 cm/year
- *β-Blocker therapy.* A randomized controlled trial of losartan versus atenolol is under way, but the results are potentially not available until 2013–14. The final N of 604 subjects was reached at the end of January 2011
- Echocardiogram every 6 months if diameter is >2 standard deviation (SD) in an adult or rate of increase in size is >0.5 cm/year
- Surgical repair for measurements >4.5 cm, rate of increase in size >1 cm/year, or progressive aortic regurgitation
- Magnetic resonance angiography or CT of the entire aorta starting in young adulthood. Repeat annually if there is a history of aortic root replacement or dissection, less frequently if not

B. *Normal aortic root size with systemic involvement of another system with a positive family/genetic history:*

- Annual echocardiogram

C. *Normal aortic root size with systemic involvement with a negative family/genetic history:*

- Repeat echocardiogram every 2–3 years until adult height is reached. Then repeat if symptomatic or when a major increase in physical activity is planned. The diameter of the aortic root is slightly larger in men than women of the same body size and, in both sexes, increases very slightly and gradually in normal individuals with age, but should not exceed the general upper limit of normal of 40–42 mm, even in tall individuals.

Note: Guidelines for related disorders can be found in the Appendix in the original guideline document.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Marfan syndrome

Guideline Category

Diagnosis

Evaluation

Management

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Medical Genetics

Pediatrics

Sports Medicine

Intended Users

Physician Assistants

Physicians

Guideline Objective(s)

To provide an approach to diagnosis, evaluation, and proper long-term follow-up of individuals suspected of having Marfan syndrome

Target Population

Adolescents and adults who are suspected of having Marfan syndrome

Interventions and Practices Considered

Diagnosis

1. Physical exam
2. Family history

3. Echocardiogram
4. Dilated eye exam
5. Computed tomography (CT)
6. Magnetic resonance imaging
7. Gene sequencing
8. Imaging of the vasculature, including the cerebral vasculature
9. Magnetic resonance angiography

Management

1. β -Blocker therapy
2. Echocardiogram
3. Surgical repair for measurements
4. Magnetic resonance angiography or CT of the entire aorta
5. Calcium and vitamin D supplementation
6. Low-impact weight-bearing exercise
7. Dual energy x-ray absorptiometry (DXA) scan for height loss greater than one inch
8. Physical therapy
9. Bracing and/or surgical correction of kyphoscoliosis

Major Outcomes Considered

- Signs and symptoms of Marfan syndrome
- Clinical value of diagnostic evaluations
- Effectiveness of long term follow-up and β -blocker therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A PubMed search was performed for the time frame 1980–July 2012. Original research, case reports and reviews published in English were considered. Search terms included: Marfan, marfanoid and all of the individual conditions discussed in the guideline (Ehlers-Danlos syndrome, hypermobile type [EDS], familial thoracic aortic aneurysm and dissection, Loeys-Dietz syndrome [LDS] and other disorders of TGF β receptors, congenital contractural arachnodactyly [CCA], MASS phenotype, familial arterial tortuosity syndrome, familial mitral valve prolapse [MVP], familial ectopia lentis, bicuspid aortic valve sequence, familial tall stature, familial pectus excavatum, familial scoliosis, stickler syndrome).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Not stated

Description of Methods Used to Formulate the Recommendations

Not applicable

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of literature supporting the recommendations is not specifically stated.

Diagnostic criteria for related disorders (including Marfan syndrome) are based entirely on expert opinion, but rarely have groups of experts collaborated on refining their ideas.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate evaluation of the adolescent or adult with some features of Marfan syndrome

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- American College of Medical Genetics and Genomics (ACMG) standards and guidelines are designed primarily as an educational resource for medical geneticists and other health care providers to help them provide quality medical genetic services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the geneticists should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines.
- The entire field suffers from the lack of any systematic attempt to apply rigorous methodology to categorization.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jan

Guideline Developer(s)

American College of Medical Genetics and Genomics - Professional Association

Source(s) of Funding

American College of Medical Genetics and Genomics (ACMG)

Guideline Committee

Professional Practice and Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The author declares no conflict of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [American College of Medical Genetics and Genomics \(ACMG\) Web site](#) .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 27, 2014. The information was verified by the guideline developer on April 29, 2014.

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